Towards a New Type of Aromatic Diynes Activation : Synthesis of a Novel Bicyclic Enediyne

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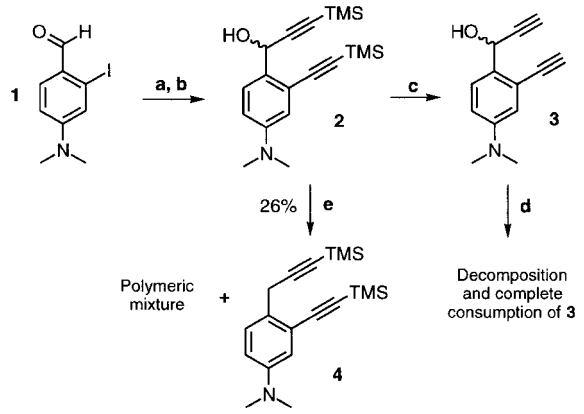
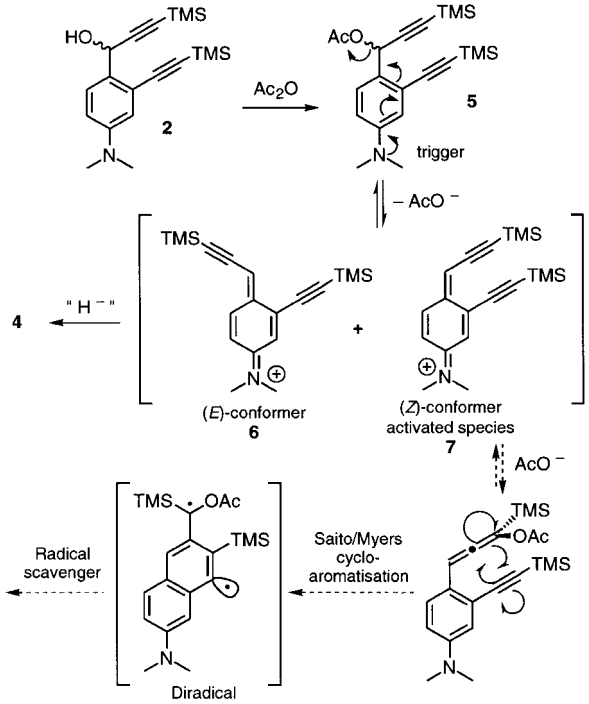
Abstract : The aromatic acyclic diynes **2** and **3** have been synthesised in order to test the feasibility of a new activation towards their cyclisation. In addition, a difference of stability between **13** and **20** during the Nozaki-Kishi cyclisation reaction occurs when the aromatic ring possesses or not an intramolecular trigger device. Thus, the aromatic bicyclic enediyne **14** is stable while **21** has not been isolated.

In our endeavour for the synthesis of cyclic enediynes[1] and dienediynes,[2] analogs of the potent antitumor natural products[3], we considered applying the prodrug concept[4] to our target molecules in order to stabilize these strongly labile compounds. Thus, we proposed a new type of activation of acyclic diynes bearing an aromatic moiety. The first step would be an intermolecular activation of the prodrug followed by the intramolecular trigger device release[5] (e.g., electron-donating group as illustrated in molecule **5**) with the aim of generating an activated species. The second step would be the addition of a nucleophile to the activated species to give rise to a diradical through a Saito/Myers cycloaromatisation.[6] This cascade reaction would allow us to reach our objective. In a preliminary study, we planned to illustrate this mode of activation on simple model compounds (Scheme 1).



Scheme 1 . **a**) TMSC≡CH (1.3 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol-%), CuI (10 mol-%), PhH, Et_3N, RT, 30 min, 96%; **b**) TMSC≡CLi (1.3 equiv.), THF, hexane, –78°C, 1 h, 59%; **c**) NH_4F (50 equiv.),*n*-Bu_4NHSO_4 (0.2 equiv.), CH_2Cl_2, H_2O, RT, 1 h, 95%; **d**) Ac_2O (2 equiv.), 1,4-cyclohexadiene (10 equiv.), pyridine (20 equiv.), 4-DMAP (5 mol-%), CH_2Cl_2, RT, 5 min, decomposition; **e**) Ac_2O (2 equiv.), 1,4-cyclohexadiene (10 equiv.), pyridine (4 equiv.), 4-DMAP (5 mol-%), CH_2Cl_2, RT, 4 h, then $NaBH_3CN$ (1 equiv.), CH_3CN, H_2O, RT, 30 min, 26% for 4

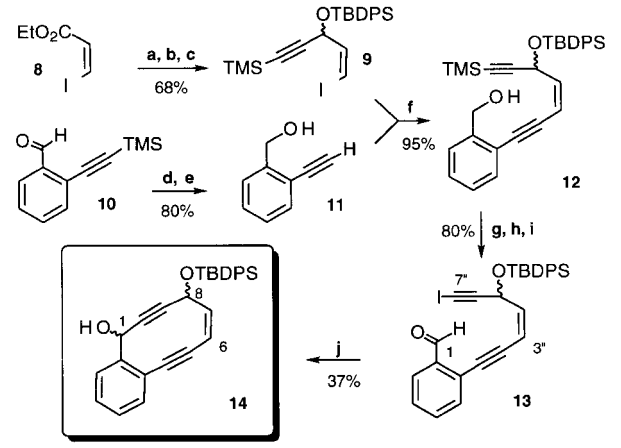
Thus, the compounds **2** and **3** were synthesised from **1** in order to investigate the feasibility of the process. Palladium catalysed cross-coupling[7] between **1** and (trimethylsilyl)acetylene is followed by the lithium (trimethylsilyl)acetylide addition to the aldehyde. The acyclic diyne **2** yielded **3** after full desilylation.[8] These compounds (**2**,**3**) proved to be fairly stable. When **3** was subjected to acylation, it was completely consumed and only decomposition was observed after a few minutes (TLC control). In contrast to compound **3**, **2** reacted slowly, (probably because of steric hindrance between both trimethylsilyl groups on the two terminal alkynes) and **4** was isolated after reduction in 26% yield. In view of this result, acylation of **2** (intermolecular activation) may lead to **5**, which can liberate an acetate molecule owing to the release of the intramolecular trigger device (dimethylamino), and generate two possible intermediates [(*E*)-conformer **6** + (*Z*)-conformer **7**]. Unfortunately, we were not able to isolate any products which would result from a Saito/Myers cycloaromatisation (Scheme 2), even in the presence of a radical scavenger.



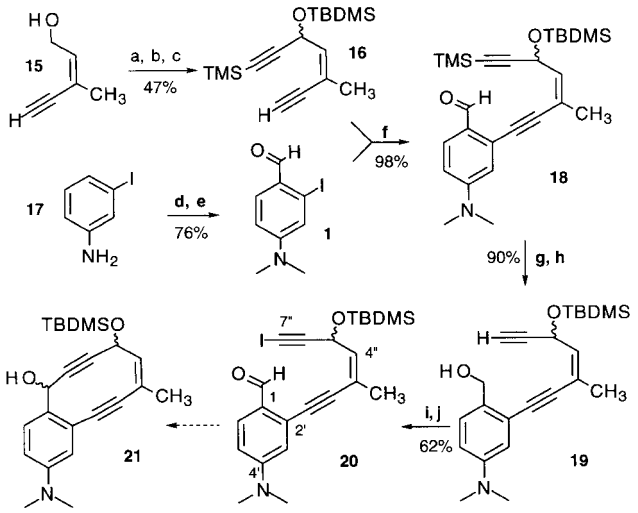
Scheme 2 . Hypothetical mechanism leading to diradical species

Thereafter, we have intended to apply this new type of activation to the cyclic enediynes **21** in order to favor the cycloaromatisation process by blocking the two acetylenic arms in a rigid cyclic system which would eventually lead to a strong interaction between the two triple bonds. In a first step, **13** was synthesised in order to study the sensitive cyclisation key step. Compound **13** was obtained from **8**[9] and **10**[10] by convergent synthesis (Scheme 3). First, ester reduction of **8** to the aldehyde ("tear oil" unstable) with Dibal-H and addition of $TMSC{\equiv}CCeCl_2$[11] followed by silylation of the alcohol with TBDPSCl gave enyne **9** in 68% yield (three steps). Reduction of **10** with $NaBH_4$ in ethanol and desilylation by phase transfer catalysis with ammonium fluoride[8] gave **11** in 80% yield (two steps). Palladium catalysed cross-coupling[7] between **9** and **11** produced aromatic acyclic enediyne **12** in very good yield. Selective monodesilylation of **12** with K_2CO_3 in methanol and iodination[12] with the presence of morpholine, followed by benzyl alcohol oxidation, using the Dess-Martin periodinane[13] afforded **13** in 80% yield (3 steps). Finally, the ring closure of **13** according to the Nozaki-Kishi reaction[14] by employing the conditions described by Eckhardt-Brückner[12b] allowed us to isolate **14** in 37% yield as a 1/1 inseparable diastereomeric

mixture. This cyclic enediyne, which does not possess a trigger device on the aromatic ring, remains fairly sensitive.



Scheme 3 . **a**) Dibal-H (1.05 equiv.) in toluene, CH_2Cl_2, –78°C, 30 min; **b**) TMSC≡CCeCl_2 (1.3 equiv.), THF, hexane, –78°C, 2 h, 68% (two steps); **c**) TBDPSCl (1.1 equiv.), imidazole (2.2 equiv.), DMF, 0°C, 2h, 100%; **d**) $NaBH_4$ (1.1 equiv.), EtOH, 0°C, 20 min; **e**) NH_4F (50 equiv.), *n*-Bu_4NHSO_4 (0.15 equiv.), CH_2Cl_2, H_2O, RT, 1 h, 80% (two steps); **f**) **9** (1.0 equiv.), **11** (1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol-%), CuI (15 mol-%), THF, *i*-Pr_2NH, RT, 2 h, 95%; **g**) K_2CO_3 (20 mol-%), MeOH, RT, 4 h, 95%; **h**) I_2 (3 equiv.), morpholine (9 equiv.), THF, 50°C, 5 h, 94%; **i**) Dess-Martin periodinane (1.3 equiv.), CH_2Cl_2, 0°C, 1 h at RT, 90%; **j**) $CrCl_2$ (3 equiv.), $NiCl_2$ (1 equiv.), THF, RT, 2 h, 37% (1/1 diastereoisomeric mixture)



Scheme 4 . **a**) activated MnO_2 (10 equiv.), CH_2Cl_2, RT, 16 h; **b**) TMSC≡CLi (2.2 equiv.), THF, hexane, –78°C, 15 min, 49% (two steps); **c**) TBDMSCl (1.5 equiv.), imidazole (2.0 equiv.), THF, RT, 12 h, 95%; **d**) HCHO 37% in water (10 equiv.), $NaBH_3CN$ (3 equiv.), CH_3CN, AcOH, RT, 3 h, 93%; **e**) $POCl_3$ (1.2 equiv.), DMF, 75°C, 3 h, 82%; **f**) **16** (1.2 equiv.), **1** (1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol-%), CuI (10 mol-%), PhH, Et_3N, RT, 1 h, 98%; **g**) K_2CO_3 (30 mol-%), MeOH, CH_2Cl_2, RT, 6 h; **h**) $NaBH_4$ (1.6 equiv.), EtOH, THF, RT, 4 h, 90% (two steps); **i**) I_2 (3 equiv.), morpholine (9 equiv.), THF, 45°C, 14 h, 65%; **j**) TPAP (5 mol-%), NMO, monohydrate (1.5 equiv.), MS 4Å, CH_2Cl_2, RT, 1 h, 95%

In the same way, **20** was obtained from **15** and **17** by convergent synthesis (Scheme 4). Commercially available allylic alcohol **15** was oxidized with activated MnO_2[15] to the aldehyde (very volatile and unstable) which immediately reacted subsequently with lithium trimethylsilylacetylide, and protected as a silylated ether to give **16** in 47% yield (three steps). Furthermore, dimethylation[16] of **17**, followed by a regioselective formylation[17] step, yielded iodo arene **1** in 76% yield (two steps). Palladium catalysed cross-coupling[7] between **16** and **1** afforded **18** in very good yield.

Desilylation of the alkyne with K_2CO_3 in methanol/dichloromethane (2/1) and reduction of the aldehyde with $NaBH_4$ in ethanol/THF (2/1) furnished the intermediate **19** in 90% yield (two steps). Finally, iodination[12] with the presence of morpholine and benzylic alcohol oxidation with TPAP[18] and NMO gave the acyclic enediyne **20**[19] in 62% yield (two steps), precursor of bicycle **21**. Unfortunately, the ring closure carried out following the conditions used for **13** led after several attemps to a complex mixture of unidentified compounds. Probably the cyclisation step occurs, however the trigger device must be activated and releases a reaction cascade.

In conclusion, a new type of aromatic acyclic diynes activation was conceived and tested on model substrates. Studies towards the synthesis and the activation in presence of a nucleophile (e. g., thiol) of these simple aromatic acyclic diynes are in progress and will be reported in due course.

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(19) All new compounds are characterized by ^{1}H and ^{13}C NMR, and microanalysis.

13 : **^{1}H NMR** ($CDCl_3$ - 200 MHz) : δ = 1.08 [s, 9H, SiC ($C\underline{H}_3)_3$], 5.50 (d, 1H, ^{3}J = 8.8 Hz, H-5"), 5.77 (d, 1H, ^{3}J = 10.5 Hz, H-3"), 6.09 (dd, 1H, ^{3}J = 10.5 Hz, ^{3}J = 8.8 Hz, H-4"), 7.12-7.69 [m, 10H, Si($\underline{Ph}$)$_2$], 7.72-7.90 (m, 4H, aromatic H), 10.13 (s, 1H, H-1). – **^{13}C NMR** ($CDCl_3$ - 50 MHz) : δ = 3.65 (C-7"), 19.26 [Si$\underline{C}$(CH_3)$_3$], 26.49 [SiC($\underline{C}H_3$)$_3$], 63.40 (C-5"), 90.93-91.11-93.14 (C-1", 2", 6"), 109.53 (C quat), 126.18-126.95-127.57-128.71-129.77 (CH), 132.75 (C quat), 133.38-133.45 (CH), 135.69 (C quat), 135.88-142.01 (CH), 191.08 (C-1). – **microanalysis** : % C (th. = 62.72, exp. = 62.81), % H (th. = 4.74, exp. = 4.87).

14 : **^{1}H NMR** ($CDCl_3$ - 200 MHz) : δ = 1.09 [s, 9H, SiC ($C\underline{H}_3)_3$, dia I], 1.11 [s, 9H, SiC($C\underline{H}_3)_3$, dia II], 2.13 (d, 1H, ^{3}J = 7.1 Hz, OH, dia I), 2.20 (d, 1H, ^{3}J = 7.6 Hz, OH, dia II), 5.09 (m, 1H, H-8, dia I), 5.17 (m, 1H, H-8, dia II), 5.23 (d, 1H, ^{3}J = 7.6 Hz, H-1, dia II), 5.40 (dd, 1H, ^{3}J = 7.1 Hz, ^{5}J = 1.7 Hz, H-1, dia I), 5.75 (d, 1H, ^{3}J = 11.7 Hz, H-6, dia I), 5.76 (d, 1H, ^{3}J = 11.7 Hz, H-6, dia II), 5.88 (dd, 1H, ^{3}J = 11.7 Hz, ^{3}J = 3.8 Hz, H-7, dia I), 5.98 (dd, 1H, ^{3}J = 11.7 Hz, ^{3}J = 2.7 Hz, H-7, dia II), 7.13-7.49 [m, 10H, Si($\underline{Ph}$)$_2$], 7.66-7.90 (m, 4H, aromatic H). – **^{13}C NMR** ($CDCl_3$ - 50 MHz) : δ = 19.22 [Si$\underline{C}$(CH_3)$_3$], 26.82 [SiC($\underline{C}H_3$)$_3$], 62.44-62.85 (C-8), 64.21-65.53 (C-1), 85.10-86.28-91.45-95.78 (C-4, 5, 9, 10), 109.78-110.55 (CH), 120.74-121.07 (C quat), 127.53-127.73-128.02-128.31-128.82-128.93-129.91-130.14-131.82 (CH), 133.09-133.17 (C quat), 134.77-135.80-136.02 (CH), 139.11 (C quat), 139.59-141.62 (CH). – **MS**, m/z (%) : 448 (26) [M^+], 391 (84), 314 (47), 252 (48), 199 (100).

– **microanalysis** : % C (th. = 76.10, exp. = 75.97), % H (th. = 6.97, exp. = 7.22).

20 : **^{1}H NMR** ($CDCl_3$ - 200 MHz) : δ = 0.15-0.17 [2 s, 6H, Si($C\underline{H}_3)_2$], 0.92 [s, 9H, SiC($C\underline{H}_3)_3$], 2.01 (d, 3H, ^{4}J = 1.3 Hz, $C\underline{H}_3$), 3.10 [s, 6H, N($C\underline{H}_3)_2$]; 5.54 (d, 1H, ^{3}J = 8.8 Hz, H-5"), 5.85 (dq, 1H, ^{3}J = 8.8 Hz, ^{4}J = 1.3 Hz, H-4") ; 6.64-6.77 ABX signal (BX part, m, 2H, H-3' and H-5'); ABX signal (A part, 1H, δ_A = 7.85, J_{AB} = 9.7 Hz, H-6'), 10.25 (s, 1H, H-1). – **^{13}C NMR** ($CDCl_3$ - 50MHz) : δ = – 4.52 [Si($\underline{C}H_3)_2$], 2.14 (C-7"), 18.33 [Si$\underline{C}$(CH_3)$_3$], 22.91 ($\underline{C}H_3$), 25.86 [SiC($\underline{C}H_3)_3$], 40.10 [N($\underline{C}H_3)_2$], 63.57 (C-5"); 91.55-92.12-94.35 (C-1", 2", 6"), 111.90 (C-5'), 114.43 (C-3'), 119.82 (C-3"), 124.81-128.08 (C-1', 2'), 129.38 (C-6'), 137.00 (C-4"), 153.46 (C-4'), 189.42 (C-1).

– **microanalysis** : % C (th. = 54.43, exp. = 54.56), % H (th. = 5.96, exp. = 6.02), % N (th. = 2.76, exp. = 2.73).